Fgf10 overexpression enhances the formation of tissue-engineered small intestine.

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Public Summary:
Short bowel syndrome (SBS) is a morbid and mortal condition characterized in most patients by insufficient intestinal surface area. Current management strategies are inadequate, but tissue-engineered small intestine (TESI) offers a potential therapy. A barrier to translation of TESI is the generation of scalable mucosal surface area to significantly increase nutritional absorption. Fibroblast growth factor 10 (Fgf10) is a critical growth factor essential for the development of the gastrointestinal tract. We hypothesized that overexpression of Fgf10 would improve the generation of TESI. Organoid units, the multicellular donor tissue that forms TESI, were derived from Rosa26rtTA/+ , tet(o)Fgf10/- or Fgf10Mlc-nlacZ-v24 (hereafter called Fgf10lacZ) mice. These were implanted into the omentum of NOD/SCID gamma-chain-deficient mice and induced with doxycycline in the case of tet(o)Fgf10/- . Resulting TESI were explanted at 4 weeks and studied by histology, quantitative RT-PCR and immunofluorescence. Four weeks after implantation, Fgf10 overexpressing TESI was larger and weighed more than the control tissues. Within the mucosa, the villus height was significantly longer and crypts contained a greater percentage of proliferating epithelial cells. A fully differentiated intestinal epithelium with enterocytes, goblet cells, enteroendocrine cells and Paneth cells was identified in the Fgf10-overexpressing TESI, comparable to native small intestine. beta-Galactosidase expression was found in both the epithelium and the mesenchyme of the TESI derived from the Fgf10LacZ duodenum. However, this was not the case with TESI generated from jejunum and ileum. We conclude that Fgf10 enhances the formation of TESI. Copyright (c) 2013 John Wiley & Sons, Ltd.

Scientific Abstract:
Short bowel syndrome (SBS) is a morbid and mortal condition characterized in most patients by insufficient intestinal surface area. Current management strategies are inadequate, but tissue-engineered small intestine (TESI) offers a potential therapy. A barrier to translation of TESI is the generation of scalable mucosal surface area to significantly increase nutritional absorption. Fibroblast growth factor 10 (Fgf10) is a critical growth factor essential for the development of the gastrointestinal tract. We hypothesized that overexpression of Fgf10 would improve the generation of TESI. Organoid units, the multicellular donor tissue that forms TESI, were derived from Rosa26rtTA/+ , tet(o)Fgf10/- or Fgf10Mlc-nlacZ-v24 (hereafter called Fgf10lacZ) mice. These were implanted into the omentum of NOD/SCID gamma-chain-deficient mice and induced with doxycycline in the case of tet(o)Fgf10/- . Resulting TESI were explanted at 4 weeks and studied by histology, quantitative RT-PCR and immunofluorescence. Four weeks after implantation, Fgf10 overexpressing TESI was larger and weighed more than the control tissues. Within the mucosa, the villus height was significantly longer and crypts contained a greater percentage of proliferating epithelial cells. A fully differentiated intestinal epithelium with enterocytes, goblet cells, enteroendocrine cells and Paneth cells was identified in the Fgf10-overexpressing TESI, comparable to native small intestine. beta-Galactosidase expression was found in both the epithelium and the mesenchyme of the TESI derived from the Fgf10LacZ duodenum. However, this was not the case with TESI generated from jejunum and ileum. We conclude that Fgf10 enhances the formation of TESI. Copyright (c) 2013 John Wiley & Sons, Ltd.